Remarks

Claims 2, 12-21, 24-25, and 27 are pending.

Claims 2, 12, 13, 16, 18, 19, 24, 25, and 27 have been cancelled without prejudice. Applicants reserve the right to prosecute the subject matter of these claims in a continuation, continuation-in-part, or divisional application of this Application.

Claims 14, 15, 17, and 20 have been amended. Pursuant to the provisions of 37 C.F.R. §1.121(c)(1)(ii), a marked-up copy of claims 14, 15, 17, and 20 is attached herewith as Appendix A.

Claims 14, 15, and 20 have been amended to depend upon a currently pending claim.

Claim 14 has also been amended to clarify that the hybridoma that produces the binding agent (and not the binding agent itself) has been deposited with the American Type Culture Collection. Support for this claim amendment can be found in the specification at page 18, lines 6-7.

Claim 17 has been amended to clarify that the immune response is induced to prostate specific antigen and that the binding agent is administered to a patient. Support for these claim amendments can be found throughout the specification (*e.g.*, at page 12, lines 14-15).

Claim 17 has also been amended to incorporate the limitations of claim 13, which has been cancelled without prejudice.

The claims have also been amended to correct regretted typographical errors.

The specification has also been amended. Pursuant to the provisions of 37 C.F.R. §1.121(b)(1)(iii), a marked-up copy of claims 14, 15, 17, and 20 is attached herewith as Appendix B.

The title of the Application has been changed to more clearly reflect the subject matter of the pending claims. Enclosed herewith is a Request for Corrected Filing Receipt.

The specification has been amended at page 21 to bring the specification into compliance with the 37 C.F.R. §1.821-1.825.

The specification has been amended at page 29, line 9, to clarify that the mice in experiment 8 are Balb/c mice and that the mice in experiment 9 are DBA mice. Support for these amendments can be found in the specification at page 30, line 3; at page 32, line 12; and at page 36, line 17.

The specification has also been amended at page 31, line 20, to correct the typographical error which refers to figure 7. Support for this amendment can be found in the specification at, for example, page 8, lines 24-26; page 25, lines 20-23; and in Figure 7 as originally filed.

None of the above amendments to the claims or the specification adds any new matter.

Each of the rejections and objections set forth in the Office Action is addressed separately below.

I. The Application Is Entitled To The Filing Date of the Priority Document

Applicants respectfully aver that the Application is entitled to the filing date, June 15, 1998, of the priority document, U.S. Provisional Patent Application Serial No. 60/089,281.

Specifically, Applicants respectfully direct the Examiner's attention to the priority document at page 16, line 18 through page 17, line 2. There, the priority document discloses a method for inducing an immune response to PSA by mixing a binding agent with patient's blood or serum ex vivo, and then returning the binding agent-added blood or serum to the patient. Similarly, at page 18, line 22 through page 19, line 2, the priority document describes the ability of a binding agent/antigen complex to bind antigen presenting cells. As the priority document teaches at page 12, lines 2-5, this complex of binding agent/antigen is capable of inducing an immune response in the patient.

Moreover, the Examples of the priority document (at page 19, lines 13 through page 26, line 1) provide additional support for the claims of the Application. (Indeed, the examples of the priority document are identical to the first eight examples of the Application.) For example, Examples 1-3 (priority document at page 19, line 13 through page 21, line 17) describe the generation of hybridoma cell line AR47.47, which produces the preferred anti-PSA antibody of the invention. Example 7 (priority document at page 24, line 13 through page 25, line 7) describes the reduction in tumor burden in mice immunized with an anti-PSA antibody, as compared to those mice immunized with control antibody.

Applicants aver that the priority document fully supports the currently pending claims of the Application. As discussed below, the hybridoma cell line producing the preferred anti-PSA antibody of the invention, AR47.47, was deposited with the American Type Culture Collection in accordance with the Budapest Treaty on the International Recognition of the Deposit of

Microorganisms for the Purposes of Patent Procedure prior to the filing date of the priority document.

Thus, Applicants respectfully request that the Application be granted the benefit of the June 15, 1998 filing date of the priority document, U.S. Provisional Patent Application Serial No. 60/089,281.

II. The Claims Are Not Objectionable

As to claim 14, Applicants have presently amended this claim to remove the period (.) appearing in this claim.

As to claims 12 and 19, Applicants have presently canceled these claims without prejudice.

Accordingly, Applicants respectfully aver that the claims as amended are not objectionable.

III. The Application Complies With The Sequence Rules

Applicants respectfully aver that the Application complies with the sequence rules as set forth in 37 C.F.R. §1.821-1.825.

As the objection applies to claims 24 and 25, Applicants have herewith cancelled these claims without prejudice. Accordingly, this objection, which has now been rendered moot, can be withdrawn.

As this objection applies to the specification, Applicants have amended the specification at pages 11 and 21 such that the amino acid sequences listed thereon are accompanied by their sequence identification numbers. Accordingly, this ground for rejection should be reconsidered and withdrawn.

IV. The Application Complies with the Deposit Requirement

Applicants respectfully aver that the hybridoma cell line, AR47.47, was deposited with the American Type Culture Collection on April 29, 1998, in accordance with the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. As evidenced by the receipt received from the American Type

Culture Collection (copy attached herewith as Appendix C), the culture was tested for and found to be viable on June 1, 1998, and was assigned ATCC Designation No. HB-12526. Applicants note that July 1, 1998 is prior to the earliest priority date, June 15, 1998, claimed by the Application.

Applicants further information regarding the deposition of the AR47.47 cell line with the American Type Culture Collection can be found in the specification at page 18, lines 6-7.

Accordingly, Applicants respectfully aver that the Application complies with the deposit requirement.

V. The Claims Are Patentable Under 37 C.F.R. §112, Second Paragraph

The claims stand rejected under 37 C.F.R. §112, second paragraph, as being indefinite. Specifically, claim 19 stands rejected for failing to include an administering step.

Claim 19 has been canceled without prejudice. Accordingly, this ground for rejection should be reconsidered and withdrawn.

Claims 24 and 25 stand rejected because it is asserted that the ordinarily skilled artisan could not have determined which amino acids comprise the claimed amino acids numbered 135-150 of human prostate specific antigen, and because they include specific amino acid residue numbers. As claims 24 and 25 have been canceled without prejudice, this ground for rejection is rendered moot. Accordingly, Applicants respectfully request that this ground for rejection be reconsidered and withdrawn.

Claim 2 and dependent claims 12-21, 24-25, and 27 stand rejected for failing to recite a step correlating to an administration step. As claim 2 has been canceled without prejudice, this ground for rejection is rendered moot. Accordingly, Applicants respectfully request that this ground for rejection be reconsidered and withdrawn.

VI. The Claims Are Patentable Under 37 C.F.R. §112, First Paragraph

The Office Action has asserted that the claims are neither enabled by the specification nor commensurate in scope with the disclosure.

A. The Claims Are Enabled by The Specification

The Office Action has asserted that the claims are not enabled by the specification.

Applicants respectfully traverse this ground for rejection as it pertains to the currently pending claims as presently amended.

As an initial matter, Applicants clarify that Figure 9 of the specification is meant to demonstrate that there is a negative correlation between the development of Ab3 in mice immunized with an anti-PSA antibody and the number of tumor foci in these mice (see Figure 9, far right panel). Ab3 antibodies, as the specification teaches at page 6, lines 19-21, are anti-anti-idiotypic antibodies, some of which react with the original antigen. Thus, as Figure 9, far right panel, shows, the more Ab3 antibodies the immunized mice produces, the fewer tumor foci. Only those mice that made very few Ab3 antibody has a high number of tumor foci. That the control mice did not make Ab3 is consistent with the fact that these mice were either administered only PBS (Figure 9, far left panel), or a control antibody (Figure 9, middle panel). In these control mice, production of Ab3 antibody, which binds to PSA, was likely stimulated by exposure to the tumor itself. Consequently, the more tumor foci in the control animal, the more the animal is exposed to PSA, and thus the more Ab3 antibody (which binds to PSA) the animal generates. As the specification teaches at page 36, lines 11-13, "The positive signal obtained for Ab3 in the control groups (PBS and control mab) is not surprising since the release of human PSA by the growing tumor in vivo will induce an anti-PSA immune response."

Thus, in Figure 9, Applicants have demonstrated that immunization with an anti-PSA antibody will generate Ab3 antibodies, and that those animals that generate Ab3 antibodies have fewer tumor foci compared with those animals who do not generate Ab3 antibodies. Thus, administration of the anti-PSA binding agent according to the invention can stimulate an immune response in the animal that includes generation of Ab3 antibodies and so reduces the number of tumor foci in the animal.

Applicants respectfully aver that the currently pending claims, which are drawn to a method of inducing an immune response to prostate specific antigen by administering to a patient a binding agent that specifically binds to an epitope of circulating prostate specific antigen that includes the sequence of SEQ ID NO:1, where the binding agent is able to bind to the antigen to form an immunogenic binding agent-antigen complex, are fully enabled by the specification.

The Application sets forth several examples demonstrating that administration of a binding agent that specifically binds to amino acid residues 139-163 (*i.e.*, SEQ ID NO: 1) in prostate specific antigen induces an immune response to prostate specific antigen. As discussed above, the results shown in Figure 9 demonstrate that administration of the binding agent induces the production of Ab3 antibodies which bind to prostate specific antigen. Examples 10 and 11 (specification, page 31, line 1 through page 36, line 13) further demonstrate that before tumor inoculation, administration of AR47.47-KLH induces more Ab3 antibody production in both Balb/c and DBA mice as compared to these mice administered PBS or control MAb-KLH. Moreover, after tumor inoculation (*i.e.*, after increased exposure of the mice to PSA), all mice immunized with AR47.47-KLH in all experimental groups generated Ab3 antibody; however, not all mice immunized with only PBS or control MAb-KLH generated Ab3 antibody following tumor inoculation.

As a final matter, Applicants note that, as stated in the specification at page 27, line 12-13, only some of the Ab3 response is identical in terms of specificity to the epitope specifically bound by AR47.47. Thus, as required by the currently pending claims, the Application teaches that administration of a binding agent that specifically binds an epitope on PSA that includes SEQ ID NO:1 will generate an immune response to PSA.

Applicants aver that these results clearly demonstrate that administration of an anti-PSA binding agent, reliably induces an immune response to prostate specific antigen. Thus, Applicants aver that the currently pending claims, as presently amended, are fully enabled by the specification of the Application. Accordingly, Applicants request that this ground for rejection be reconsidered and withdrawn.

B. The Claims Are Commensurate In Scope With The Disclosed Invention

The Office Action has asserted that the claims are not commensurate in scope with the disclosure.

Applicants respectfully traverse this ground for rejection as it pertains to the currently pending claims as presently amended.

The currently pending claims require the induction of an immune response to prostate specific antigen by administering to a patient a binding agent that specifically binds to an epitope

of circulating prostate specific antigen that includes the sequence of SEQ ID NO:1, where the binding agent is able to bind to the antigen to form an immunogenic binding agent-antigen complex. As taught in the specification, particularly in Example 6 (specification page 26), Example 7 (specification page 26-27), Example 8 (specification page 27), Example 10 (specification page 31-32), and Example 11 (specification page 32-36), administration of a binding agent that specifically binds to an epitope including SEQ ID NO:1 induces an anti-PSA immune response.

Applicants respectfully aver that the claims, which require induction of an immune response to PSA by administration of a binding agent that specifically binds an epitope including SEQ ID NO:1, are commensurate in scope with the disclosure. That the binding agent can form a complex with the antigen is evidenced by the method by which AR47.47 was generated and selected for (see Example 1, specification page 15-18). That the complex is immunogenic is evidenced by the increased Ab3 antibody in mice administered AR47.47 plus tumor inoculation, as compared to mice administered PBS or control antibody plus tumor inoculation. The increased Ab3 production in the mice administered AR47.47 plus tumor inoculation demonstrates that some AR47.47 must be forming an immunogenic complex with PSA, and that this immunogenic complex is missing in the PBS or control antibody-administered mice, thereby decreasing their ability to generate Ab3 antibody.

Thus, Applicants aver that the currently pending claims, as presently amended, are commensurate in scope with the disclosure. Accordingly, Applicants request that this ground for rejection be reconsidered and withdrawn.

VII. The Claims Are Patentable Under 37 C.F.R. §102(b)

Claims 2, 12, 13, 15-19, and 24-25 stand rejected as being anticipated by Giri et al., European Patent Application No. 0 652 014 (hereinafter "Giri").

Although claims 2, 12, 13, 16, 18, 19, 24, and 25 have been presently canceled without prejudice, Applicants address this rejection as it applies to the pending claims.

As this rejection applies to independent claim 17, and to the non-cancelled claims dependent thereon (*i.e.*, claims 14, 15, 20, and 21), Applicants have overcome this ground for rejection by the present amendment to 17, which requires that the binding agent specifically bind

an epitope comprising the sequence of SEQ ID NO: 1. As Giri nowhere teaches a binding agent that specifically binds to an epitope comprising the sequence of SEQ ID NO:1, the claims, as amended, are no longer anticipated by Giri. Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground for rejection of the claims.

VIII. The Claims Are Patentable Under 37 C.F.R. §103(a)

Claims 2, 12, 13, 20-21, and 27 stand rejected as being unpatentable over Giri in view of Masuzawa et al., *Neuroscience Res.* **18**: 27-34, 1993 (hereinafter "Masuzawa").

Applicants have canceled claims 2, 12, 13, and 27; accordingly, this rejection will be addressed as it applies to claims 20 and 21.

Applicants have presently amended claim 17 to require a binding agent that specifically binds an epitope comprising the sequence of SEQ ID NO: 1. As claims 20 and 21 are dependent upon claim 17, they likewise require a binding agent that specifically binds an epitope comprising the sequence of SEQ ID NO:1.

As discussed above, Giri nowhere teaches a binding agent that specifically binds to an epitope comprising the sequence of SEQ ID NO:1. Moreover, nowhere does Giri even suggest such a binding agent having the specificity set forth in the amended claim.

Nor do the teachings of Masuzawa do not cure this deficiency—nowhere does Masuzawa teach or suggest a binding agent that specifically binds to an epitope comprising the sequence of SEQ ID NO:1. In fact, nowhere does Mazuwa teach or suggest a binding agent that specifically binds to any epitope of prostate specific antigen.

Since neither Giri nor Masuzawa teach or suggest a binding agent that specifically binds to an epitope comprising the sequence of SEQ ID NO:1, as is required by the claims, their combination (even if the ordinarily skilled artisan were motivated to combine their teachings) cannot teach or suggest such a binding agent. Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground for rejection.

Conclusions

In accordance with the provisions of 37 C.F.R. §1.136(a)(1), Applicants enclose herewith a petition requesting a three month extension of time up to and including March 5, 2001 to respond to the Office Action mailed September 5, 2000.

No additional fees are believed to be due in connection with this communication. However, please apply any additional charges, or credit any overpayment, to our Deposit Account No. 08-0219.

Respectfully submitted,
HALE AND DORR LLP

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APPENDIX A

Marked-up Version of the Amended Claims Pursuant to 37 C.F.R. §1.121(c)(1)(ii)

14. (Amended) The method of claim [12] 17 wherein the [composition comprises a] binding agent is produced by a hybridoma that has ATCC Accession [No. 12526] Number HB-12526.

15. (Amended) The method of claim [12] 17 wherein the [therapeutic] immune response comprises a humoral and cellular immune response.

17. (Amended) A method for inducing an immune response to prostate specific antigen comprising administering a binding agent to a patient, wherein the binding agent [that] specifically binds to an epitope of circulating prostate specific antigen, the epitope comprising the sequence of SEQ ID NO:1, the binding agent being capable of binding to the antigen to form an immunogenic binding agent-antigen complex.

20. (Amended) The method[s] of claim [12] 17 wherein the binding agent is conjugated to an immunogenic carrier.

APPENDIX B

Marked-up Version of the Amended Specification Pursuant to 37 C.F.R. §1.121(b)(1)(iii)

At page 1, lines 1-2

[IMMUNOTHERAPEUTIC COMPOSITION] REAGENTS AND METHODS FOR [THE TREATMENT OF] INDUCING AN IMMUNE RESPONSE TO PROSTATE [CANCER] SPECIFIC ANTIGEN

At page 21, lines 7-10:

PSA 139-163	EEFLTPKKLQCVDLHVISNDVCAQV	(SEQ ID NO: 1)
PSA 141-150	FLTPKKLQCV	(SEQ ID NO: 2)
PSA 146-154	KLQCVDLHV	(SEQ ID NO: 3)
PSA 154-163	VISNDVCAQV	(SEQ ID NO: 4)

At page 29, lines 8-15:

Experiment #	5	6	7	8	9
mice	Balb/c	DBA	Balb/c	Balb/c [DBA]	DBA [Balb/c]
# mice/group	10	10	5	5	5
Therapeutic anti-PSA MAb	47.47R6R6	47.47R6R6	47.47R6R6	47.47R6R6	47.47R6R6
Control MAb	MOPC	MOPC	CA125 MAb	CA125 MAb	MOPC
form of injected MAb	KLH conjugate	KLH conjugate	KLH conjugate	KLH conjugate	KLH conjugate

At page 31, line 14 through page 32, line 2:

Two different ELISA assays were performed to detect the presence of Ab3. The first assay detects the binding of Ab3 on PSA coated plate. Using this assay, we have demonstrated in experiments # 5, 6 and 7 the presence of Ab3 in the sera of mice immunized with AR 47.47. The second assay employs the PSA peptide known to be recognized by AR 47.47. This assay gave positive signal for the mice immunized with AR 47.47 in experiment 7. This second assay however has not been standardized at this time and the results [shown in figure 7] should be analyzed with caution since in many cases the positive control (performed with AR 47.47) showed negative signal. Since the PSA peptide used for this assay contains cysteine residues we believed that a cyclisation or polymerization of the peptide occurs after solubilization and/or storage of the peptide. Such effect may impairs the binding of the peptide to streptavidin coated plate or to specific antibodies (i.e., AR 47.47 or Ab3).

APPENDIX C

ATCC

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

University of Alberta
Attn: Dr. B. Leveugle
3118 Dentistry Pharmacy CTR
Edmonton, Alberta T6G 2N8
Canada

Deposited on Behalf of: AltaRex Corp.

Identification Reference by Depositor:	**ATCC Designation**
Mouse hybridoma AR 47.47	HB-12526

The deposit was accompanied by: ___ a scientific description __ a proposed taxonomic description indicated above. The deposit was received April 29, 1998 by this International Depository Authority and has been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested June 1, 1998. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Barbara M. Hailey

Barbara M. Hailey, Administrator, Patent Depository

Date: June 24, 1998

cc: William J. Bundren (Ref. Docket A52026)